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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/695,574 | 10/28/2003 | Denis Barritault | 1003-DIV-01 | 4857 |

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| EXAMINER | |
|---|---|
| FERNANDEZ, SUSAN EMILY | |
| **ART UNIT** | **PAPER NUMBER** |
| 1651 | |

DATE MAILED: 11/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/695,574 | BARRITAULT ET AL. | |
| | Examiner | Art Unit | |
| | Susan E. Fernandez | 1651 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *42, 43, 61, and 62* is/are pending in the application.

4a) Of the above claim(s) *43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42, 61, and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *42,43,61 and 62* are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-28-2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The preliminary amendment filed on December 29, 2003, has been received and entered. Claims 42, 43, 61, and 62 are pending and are presented for examination.

### *Election/Restrictions*

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 42, 61, and 62, drawn to a process for treating and/or preventing fibroses, classified in class 514, subclass 1.

II. Claim 43, drawn to a process for regulation of proliferation of mesenchymal cells and regulation of the quality of the type of collagen that such cells secrete, classified in class 435, subclass 375.

Although there are no provisions under the section for "Relationship of Inventions" in M.P.E.P. § 806.05 for inventive groups that are directed to different methods, restriction is deemed to be proper because these methods appear to constitute patentably distinct inventions for the following reasons: Groups I and II are directed to methods that are distinct both physically and functionally, and are not required one for the other. Group I recites a method for treating and/or preventing fibroses. Group II recites a method for regulating cellular proliferation and collagen secretion. While Group II reads on a method of treatment, it also reads on a method of culturing cells in vitro. As to the extent that Group II reads on a therapeutic method, it refers to treating a different set of patients than Group I. Therefore, a search and examination of both methods in one patent application would result in an undue

burden, since the searches for the methods are not co-extensive, the classification is different, and the subject matter is divergent.

During a telephone conversation with Mr. Christenbury on November 5, 2004, a provisional election was made without traverse to prosecute the invention of Group I, claims 42, 61, and 62. Affirmation of this election must be made by applicant in replying to this Office action. Claim 43 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 42, 61, and 62 are examined on the merits.

***Specification***

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The disclosure is objected to because of the following informalities:

Starting on page 37 and through page 39, membrane cutoff threshold is given in units of $g/mole^{-1}$, which are not the proper units for molecular weight. Correction should be made to the appropriate units, g/mole, (specifically, see lines 19 and 27 of page 37, lines 16-17 and 20-21 of page 38, lines 3,8, and 12 of page 39).

Appropriate correction is required.

***Drawings***

The drawings are objected to for the following reasons: Figure 15 is labeled as "Percentage of FGF2 and **FGFβ**..." whereas the table and page 4 specify TGFβ. Figure 19 includes the French word "Rien". Finally, Figures 27-29 are unreadable. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42 and 61-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *in vitro* use of RGTA 1005, 1010, 1012, 1013, 1112, and 1113 for treating factors involved in fibroses, does not reasonably provide enablement for treating fibroses with all other AXY polymers. Furthermore, the claims recite "preventing" fibroses which encompasses preventing any and all fibroses in any situation which is not supported in the specification as such. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Regarding undue experimentation, *In re Wands*, 8 USPQ2d 1400, at 1404 (Fed. Cir. 1988) states:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. (Citations omitted).

The rejected claims are drawn to the method of treating and preventing fibroses by administering a pharmaceutical composition comprising the AXY polymer. The claims are broad enough to encompass an infinite number of polymers, of which experimentation would be required for every single variant to determine their efficacy as antifibrotic agents. The specification as filed only provides methods of making polysaccharide polymers, such as carboxymethyl dextran sulfates.

The amount of direction provided in the specification speaks only on the *in vitro* administration of polymers of the series RGTA 1000-1025 and 1110-1115 to observe their effect on growth kinetics in smooth muscle tissue cultures, as well as the synthesis

of collagens. The specification does not provide actual guidance or evidence supporting the use of the AXY polymer in treating or preventing fibroses in humans or animal models.

Furthermore, the specification does not address the actual prevention of fibroses since only tissue cultures were used to show antifibrotic effects. Though protective effects against ischemia were shown in rat models, no correlation can be made in relation to protection against fibroses. Prevention entails the complete inhibition of the onset of the disease and any manifestation of the disease entirely. Further, the reduction of fibroses does not equate the actual prevention of the disease.

In addition, in order to practice the claimed invention, a skilled artisan would first have to predict what population to treat since prevention provides that the population does not manifest the symptoms of the disease at all, then determine the effective dosage, route of administration, etc. of the composition that would prevent the disease. If unsuccessful, which is likely given the lack of guidance from the specification and prior art, a skilled artisan would have to experiment again.

Thus, a skilled artisan would have expected to have had to engage in an essentially trial and error process, with little guidance from the specification as filed, to determine suitable AXY polymers which treat and prevent every type of fibrosis. Such a trial and error process clearly constitutes undue experimentation.

Claims 42, and 61-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was

not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sough, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117 of *Vas-Cath*) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision all variations of the AXY polymer allowable, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of synthesis of all AXY polymers. Adequate written description requires more than a mere statement that it is a part of the invention and a set of methods for producing one set of polymers with a specific monomer. The compounds themselves are required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only the use of polymers following the synthesis methods as described in the specification (example, the first dextran carboxymethylation step addressed on page 30), but not the full breadth of the claims meet the written description provision of 35 U.S.C §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C §112 is severable from its enablement provision (see page 1115).

***Claim Rejections - 35 USC § 102***

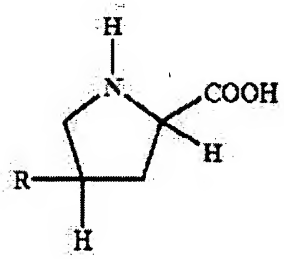
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 42, and 61-62 are rejected under 35 U.S.C. 102(e) as being anticipated by Kohn et al. (US Patent No. 6,517,824).

Kohn et al. discloses a copolymer conjugate antifibrotic composition comprising a dipeptide where one peptide has the following structure (column 45, line 55 through column 46, line 24):




where R may be $OSO_3H$.

The composition as described in Kohn fits the limitations of the claimed invention, where A is pyrrolidine, Y is $SO_3$ ($OSO_3H$ bound to A), and X is COOH

The Kohn invention is antifibrotic and is shown to inhibit the proliferation of smooth muscles cells (column 27, lines 46-56), thus anticipating claim 61 and 62. According to the specification, smooth muscle cells are considered mesenchymal cells (see page 51, lines 15 and 25). A holding of anticipation is clearly required.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan E. Fernandez whose telephone number is (571) 272-3444. The examiner can normally be reached on Mon-Fri 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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